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Toward a modular, bidirectional synthesis of (−)-mucocin

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ABSTRACT

A convergent stereoselective synthesis of the C13–C34 fragment of (−)-mucocin is described. The salient features include (a) the bidirectional synthesis of the *C*-2 symmetric C13–C21 subunit, (b) regio- and stereoselective preparation of a 1,3-diol derivative from a diene activated by NBS via intramolecular nucleophilic sulfinyl group participation, (c) utilizing the self-metathesis reaction to prepare a functionalized C10 alkene, and (d) regio- and stereoselective intermolecular epoxide opening to construct the ether bond between C20 and C24. An organocatalytic α-hydoxylation has been employed to create the C4 stereogenic center of C1–C12 subunit. Attempted union of the two subunits utilizing the *B*-alkyl Suzuki coupling did not succeed.

1. Introduction

(−)-Mucocin **1**, an annonaceous acetogenin, was isolated by McLaughlin and co-workers from the leaves of *Rollinia mucosa*.[1] Annonaceous acetogenins are polyketide derived fatty acid natural products characterized by a long chain with a terminal γ-lactone subunit, one to three tetrahydrofuran (THF) rings and carbinol chiral centers. Based on the number and the position of the THF rings the acetogenins have been classified into three subgroups: the mono-THF, the adjacent bis-THF and the non adjacent bis-THF acetogenins. Notably, mucocin was the first acetogenin shown to possess tetrahydropyran ring (THP) along with a THF ring.[2] Mucocin shows selective inhibition against A-549 (lung cancer) and PACA-2 (pancreatic cancer) solid tumor cell lines with a potency 10,000 greater than the known antitumor agent adriamycin.[3] The mode of action is through blockage of the mitochondrial complex I (NADH-ubiquinone oxidoreductase) and inhibition of the plasma membrane NADH oxidase resulting in ATP depletion and consequent apoptosis in malignant cells.[4]

2. Results and discussion

The unique structure and potent antitumor activity of mucocin make it an inviting target for total synthesis; seven total syntheses have been published till date.[5] Herein, we describe a convergent, stereoselective synthesis of the C13–C34 subunit (**2**) of mucocin by taking advantage of the nucleophilic potential of the sulfinyl group to functionalize a 1,3-diene activated by NBS as the electrophile. Mucocin was envisioned to be obtained by a *B*-alkyl Suzuki cross-coupling reaction between a vinyl iodide **3** and the trialkylborane derived from terminal alkene **2**. Compound **2** can be secured by a selective ring-closing metathesis (RCM) reaction of triene **4**, which in turn can be visualized to be obtained by the union, via ether formation (C20–O–C24), of epoxy tosylate **5** (C22–C34 subunit) and a tetrol derivative **6** (C13–C21 fragment). The diene **6** was envisioned to be obtained from diene sulfoxide **7**, Scheme 1. Construction of the THP ring system by the similar ring-closing metathesis reaction was reported by Crimmins and co-workers.[5g]

The synthesis began from diene **7**, which was readily prepared in two steps from (*S*)-methyl-*p*-tolyl sulfoxide **8**.[6] Thus the lithio anion of **8** on reaction with ethyl sorbate[7] **9** furnished the β-keto sulfoxide **10** that on diastereoselective reduction[8] using Dibal-H in the presence of anhydrous zinc chloride yielded diene alcohol **7** (dr >95:<5). The hydroxy group in **7** was protected as its *tert*-butyldimethylsilyl ether **11** and further subjected to reaction with freshly recrystallized *N*-bromosuccinimide to furnish the bromohydrin **12** as the sole product regio- and stereoselectively,[9] Scheme 2. The reaction probably proceeds via initial π-complex formation between the bromonium ion and the alkene followed by intramolecular 6-*endo* nucleophilic attack[10] by the sulfinyl group as depicted in the putative transition state **TS1**, to yield the sulfoxonium salt that on hydrolysis by attack of water at sulfur in S_N2 fashion would afford bromohydrin **12**. The alternate transition state, **TS2**, that would afford the stereoisomer of **12**, is probably not preferred for both steric and stereoelectronic reasons. 1,3-Diaxial interactions would be observed between the bulky *p*-Tol and hydrogen atoms in **TS2**, while in **TS1** diaxial interactions would be

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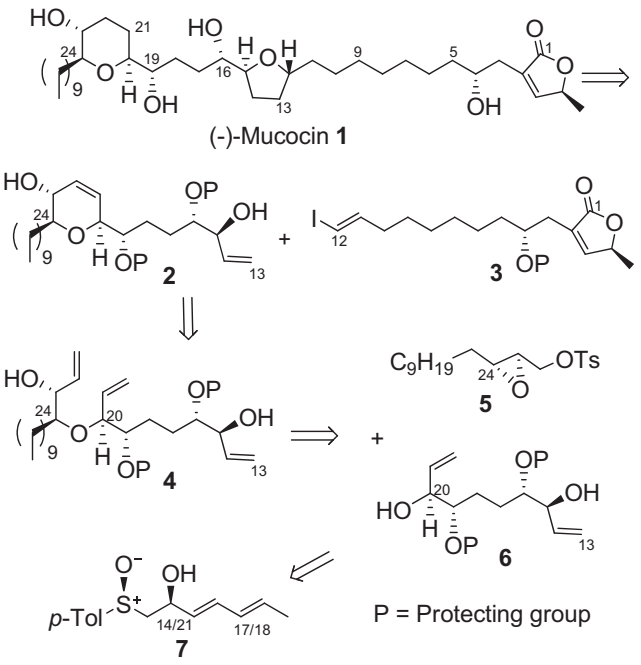
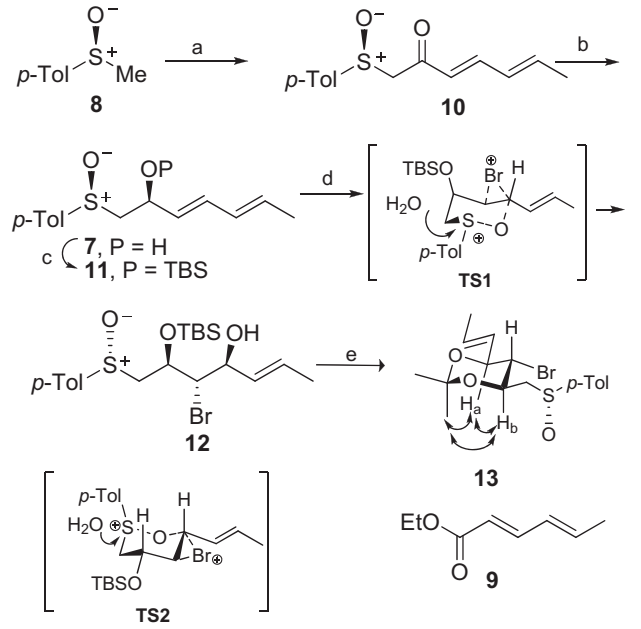


Scheme 1. Retrosynthetic analysis of (−)-mucocin.

only between OTBS and hydrogen atom. Also in TS2, with the OTBS group in the equatorial orientation, the antibonding orbitals of C–O bond are parallel to the p-orbitals of the double bond which would decrease the electron density by overlap and therefore the nucleophilicity of the alkene.[11] The structure of **12** was unambiguously proven by conversion to the acetonide **13**, obtained by deprotection of the TBS group followed by reaction with 2,2-dimethoxypropane. The *CH*Br resonated as a doublet of doublet (J=10.3, 9.5 Hz) indicating its axial orientation. Also H_a and H_b in **13** mutually show NOE with each other and also with the axial methyl group.

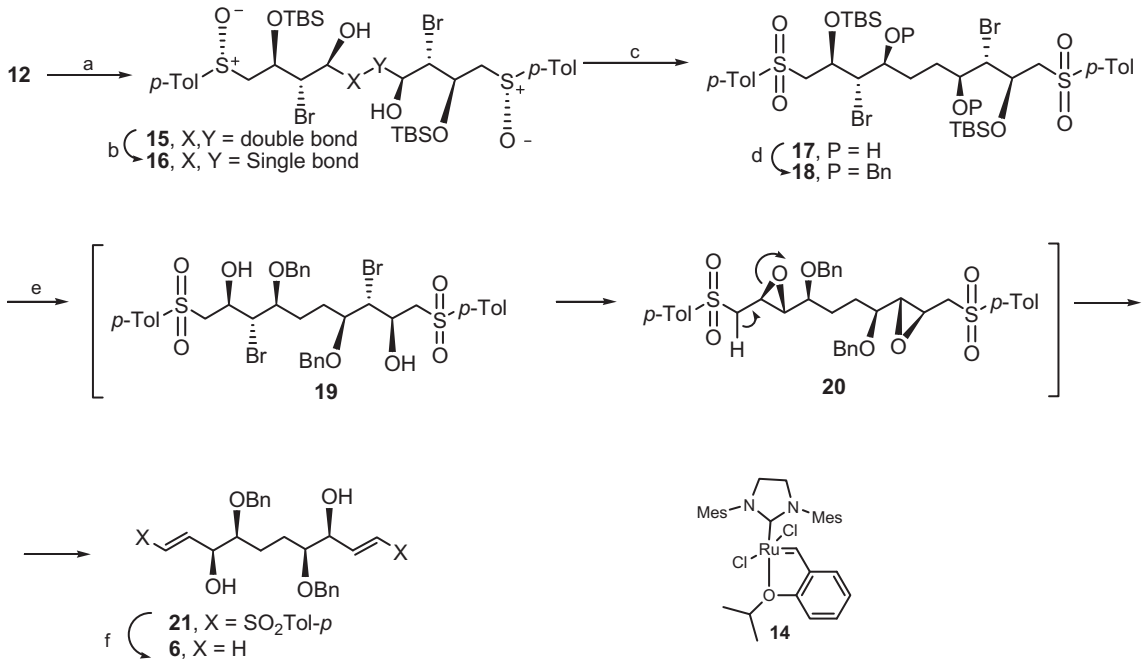


Scheme 2. Synthesis of bromohydrin **12**. Reagents and conditions: (a) LDA, THF, −40 °C, 30 min, warm to 0 °C, add **9**, 52%. (b) Dibal-H, $ZnCl_2$, THF, −78 °C, 82%. (c) TBS-Cl, imidazole, CH_2Cl_2, 0 °C to rt, 90%. (d) NBS, H_2O, toluene, rt, 76%. (e) (i) TBAF/AcOH, THF, 0 °C to rt; (ii) 2,2-dimethoxypropane, cat CSA, CH_2Cl_2, rt, 70% for two steps.

Compound **12** serves as the key intermediate in our proposed bidirectional synthesis of the C13–C34 subunit. Subjecting **12** to self metathesis[13] using Hoveyda–Grubbs catalyst[12] **14** in refluxing dichloromethane afforded the alkene **15**. It is noteworthy that alkene **15** is densely substituted with functional groups including the olefinic group which provide opportunities for further transformations. Reduction of the double bond in **15** using PtO_2/C under an atmosphere of hydrogen yielded the diol **16**. Oxidation of the sulfinyl group using *m*-CPBA afforded the sulfone **17** cleanly. Protection of the hydroxy groups as their benzyl ethers using benzyl trichloroacetamidate[14] in the presence of catalytic amounts of trifluoromethanesulfonic acid afforded **18**. It remained to displace the bromine atoms at C15, C20 and introduce hydroxy groups in its place with inversion of configuration and install terminal double bonds at C14 and C21. This was envisioned to be accomplished by a three step sequence involving, (a) desilylation of TBS ethers, (b) epoxide formation, and (c) reductive β-elimination of the resulting epoxy sulfones. In the event, treatment of **18** with TBAF furnished the vinyl sulfone **21** and none of the expected diol **19**. The formation of **21** can be rationalized by the formation of epoxide **20** from diol **19**, which suffers β-elimination due to the basicity of TBAF. Proceeding ahead, desulfonylation of **21** was attempted using Mg in ethanol[15] to yield the diene **6**. A *C*-2 symmetric ten carbon chain possessing four of the nine stereogenic centers corresponding to C13–C21 fragment of mucocin was thus obtained by a straightforward sequence of ten reactions from ethyl sorbate, Scheme 3.

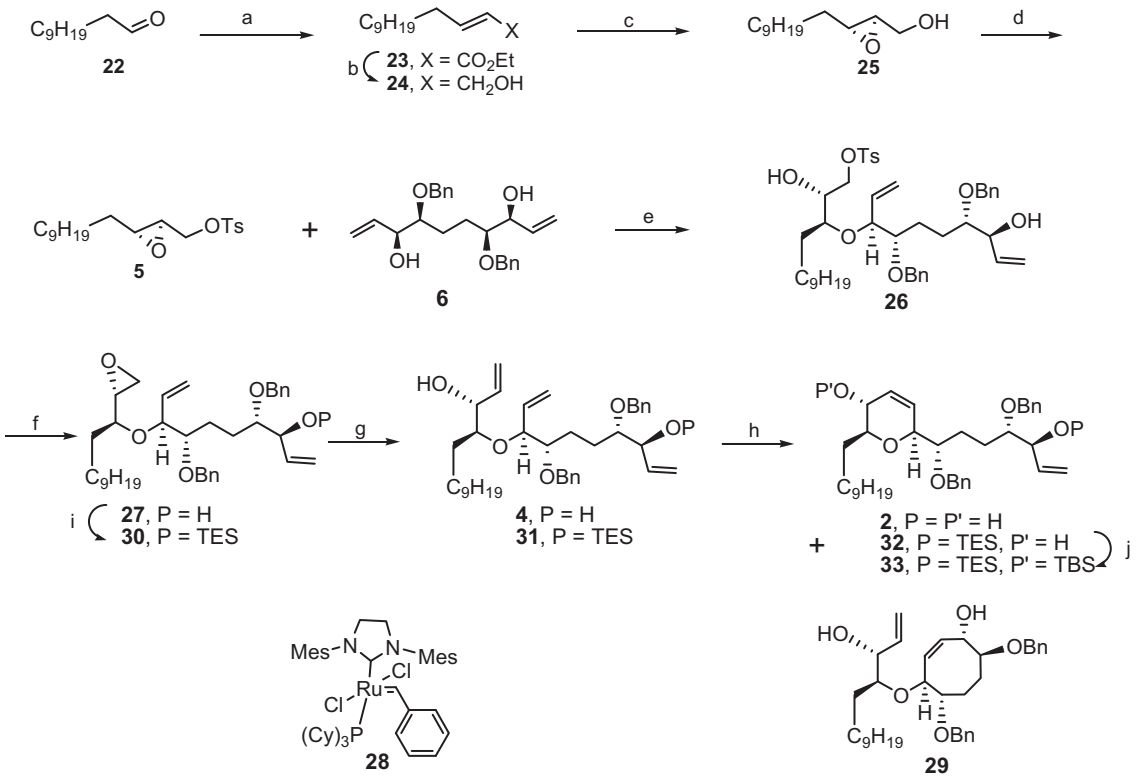
The synthon corresponding to C22–C34 fragment of mucocin was prepared starting from commercially available 1-undecanal **22**. Wittig olefination with the stable ylide Ph_3PCHCO_2Et afforded the unsaturated ester **23** that on chemoselective reduction using alane[16] furnished allylic alcohol **24**. Sharpless asymmetric epoxidation[17] using (D)-DET afforded compound **25**, which was converted following standard conditions into tosylate **5**, Scheme 4. With both the coupling partners becoming available, opening of **5** by **6** was attempted in the presence of $BF_3\cdot Et_2O$ as the catalyst using slightly modified conditions known in the literature,[18] to afford the coupled product **26** regioselectively. Epoxide formation using anhydrous potassium carbonate in a mixture of acetonitrile and methanol yielded **27**. The triene precursor **4** for the RCM reaction, was obtained by treatment of **27** with an excess of ylide generated from trimethylsulfonium iodide and *n*-BuLi.[19] The RCM reaction proceeded cleanly in the presence of Grubbs' catalyst **28**[20] to yield dihydropyran **2** (38%) and cyclooctene derivative **29** (38%) resulting from the metathesis of C13–C21 alkenes,[21] Scheme 4. The undesired product **29** was avoided by protection of the hydroxy group in **27** as its TES ether **30** using standard reaction conditions. Opening of the epoxide with the sulfur ylide furnished triene **31**. RCM reaction using **28** proceeded cleanly to afford the dihydropyran **32**. Protection of the hydroxy group using TBS/OTf and 2,6-lutidine furnished the TBS ether **33**, Scheme 4. Thus, the C13–C34 subunit of mucocin was synthesized in 16 steps by the longest linear sequence.

The synthesis of the C1–C12 subunit **3**, commenced from the known[22] acetylenic alcohol **34**. Swern oxidation[23] afforded the aldehyde **35** that was subjected to α-hydroxylation using Zhong's protocol[24] in the presence of (L)-proline to yield diol **36** after in situ reduction and subsequent N–O bond cleavage.[25] Selective transformation of the primary hydroxy group to a triflate and the secondary hydroxy group as its TBS ether was achieved in an one-pot operation by treatment with triflic anhydride followed by TBS/OTf in the presence of 2,6-lutidine to afford compound **38**. Alkylation[26] of the lithio anion of lactone[27] **39** with **38** furnished a diastereomeric mixture of sulfides **40**.[28] Oxidation of the sulfide to sulfoxide and thermal elimination of phenyl sulfenic acid yielded butenolide **41**. The terminal alkyne **41** was converted to bromo alkyne **42** by reaction with *N*-bromosuccinimide in the presence of

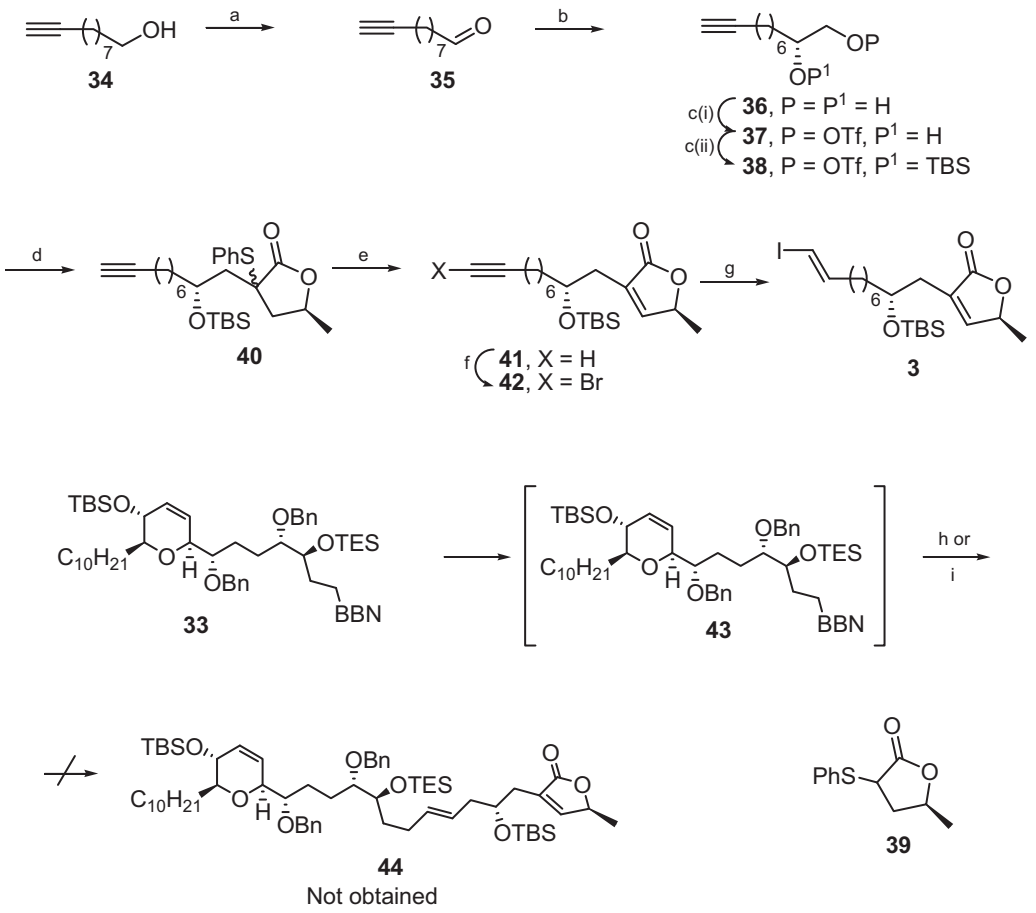


Scheme 3. Synthesis of C13–C21 fragment. Reagents and conditions: (a) 3 mol % **14**, CH_2Cl_2, reflux, 95% (based on recovered sm, 80% conversion). (b) PtO_2, H_2, 10 bar, MeOH/PhH (1:1), rt, 80%. (c) *m*-CPBA, CH_2Cl_2, 0 °C to rt, 80%. (d) $Cl_3C(NH)OBn$, cat TfOH, CH_2Cl_2/cyclohexane, 0 °C to rt, 70%. (e) TBAF, THF, 0 °C to rt, 72%. (f) Mg, cat $HgCl_2$, EtOH, 0 °C to rt, 70%.

$AgNO_3$.[29] Compound **42** on treatment[30] with *n*-Bu_3SnH and $PdCl_2(PPh_3)_2$ furnished[31] an intermediate vinyl stannane that on treatment with iodine furnished regioselectively the iodo alkene **3**, Scheme 5. With both the coupling partners **3** and **33** becoming available, their union using *B*-alkyl Suzuki reaction was attempted. Thus, treatment of **33** with 9-BBN dimer afforded the triorganoborane **43** that was subjected to reaction with compound **3** in the presence of $Pd(PPh_3)_4$ and K_3PO_4.[32] A complex mixture of products resulted. Attempted Suzuki coupling using $PdCl_2(dppf)$[33] and Cs_2CO_3 also did not yield any desired product[34] **44**, Scheme 5.



Scheme 4. Selective RCM reaction of triene **32**. Reagents and conditions: (a) Ph_3PCHCO_2Et, PhH, 80 °C, 80%. (b) AlH_3, Et_2O, 0 °C to rt, 75%. (c) (D)-DET, $Ti(O^iPr)_4$, *t*-BuOOH, CH_2Cl_2, −20 °C, 80%. (d) Ts-Cl, Et_3N, cat DMAP, CH_2Cl_2, 0 °C to rt, 90%. (e) $BF_3{\cdot}Et_2O$, CH_2Cl_2, 0 °C to rt, 70%. (f) K_2CO_3, EtOH/AcCN (1:1), rt, 90%. (g) Me_3SI, *n*-BuLi, THF, −10 °C to rt, 70%. (h) 5 Mole % **28**, CH_2Cl_2, reflux, 76% of **2** and **29** from **4**, 85% of **32** from **31**. (i) TES-Cl, Imidazole, CH_2Cl_2, 0 °C to rt, 90%. (j) TBSOTf, 2,6-lutidine, CH_2Cl_2, −78 °C, 85%.



Scheme 5. Synthesis of iodo alkene **3** and its attempted coupling with alkene **33**. Reagents and conditions: (a) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, 30 min then add Et_3N, −78 °C to rt, 90%. (b) (i) PhNO, 20 mol % L-proline, DMSO, rt; (ii) $NaBH_4$, EtOH, 0 °C; (iii) $CuSO_4 \cdot 5H_2O$, MeOH, rt, 53% overall. (c) (*i*) Tf_2O, 2,6-lutidine, CH_2Cl_2, −50 °C; (ii) TBSOTf, −50 °C to 0 °C, 93% overall. (d) LiHMDS, THF, HMPA, add **39**, −78 °C to rt, 65%. (e) (i) *m*-CPBA, CH_2Cl_2, 0 °C; (ii) Na_2CO_3, toluene, 80 °C, 76% overall. (f) NBS, 10 mol % $AgNO_3$, acetone, rt, 75%. (g) *n*-Bu_3SnH, $PdCl_2(PPh_3)_2$, 0 °C, cool to −78 °C add I_2, 70% overall. (h) (i) 9-BBN dimer, THF; (ii) **3**, $Pd(PPh_3)_4$, K_3PO_4, Dioxane, 85 °C (i) (i) 9-BBN dimer, THF; (ii) **3**, $PdCl_2$(dppf), Cs_2CO_3, Ph_3As, rt.

3. Conclusion

In summary, we have described a highly stereoselective convergent route to the C13–C34 subunit **33**, of mucocin. An organocatalytic aminoxylation reaction was employed to create the C4 stereogenic center in iodo alkene **3**. The coupling of subunits **3** and **33** envisioned by utilizing the *B*-alkyl Suzuki reaction, failed. The key steps in the synthesis of the C13–C34 fragment include the regio- and stereoselective 1,3-diol formation by intramolecular sulfinyl group participation from 1,3-diene via 1,2-functionalization without any complication arising due to competing 1,4-functionalization, self metathesis reaction to prepare a highly functionalized *C*2-symmetric molecule, which has the 1,4-diol moiety, a common structural feature of acetogenins, regioselective intermolecular opening of an epoxy tosylate and a selective RCM reaction for the formation of the THP ring. The key steps in the synthesis of compound **3** include alkylation using the triflate and regioselective stannation of the bromo alkyne **41**. A revised synthetic plan is being explored to unite subunits related to **33** and **3** to complete the synthesis of mucocin.

4. Experimental

4.1. General remarks

All air or moisture sensitive reactions were carried out under nitrogen atmosphere. Solvents were distilled over Na/benzophenone ketyl for THF, over P_2O_5 followed by CaH_2 for DCM, and over P_2O_5 for toluene. Commercially available reagents were used without purification. Thin layer chromatography was performed on precoated silica gel plates. Column chromatography was carried out using silica gel (60–120 mesh). NMR spectra were recorded on a 200, 300 or 400 MHz spectrometer. ^1H and ^{13}C NMR samples were internally referenced to TMS (0.00 ppm). Melting points are uncorrected.

4.1.1. (3E,5E)-(1Ss)-(p-Tolylsulfinyl)hepta-3,5-dien-2-one ***[10]****.* To a solution of diisopropyl amine (7 mL, 55 mmol) in dry THF (275 mL) cooled at 0 °C under nitrogen atmosphere was added *n*-BuLi (23 mL, 2.4 M in hexanes, 55 mmol) dropwise and the mixture stirred for 15 min. The solution of LDA thus generated was cooled to −40 °C and a solution of (*S*)-methyl-*p*-tolyl sulfoxide **8** (3.85 g, 25 mmol) in anhydrous THF (200 mL) was added dropwise over 5 min. The reaction mixture was stirred for 30 min and warmed to 0 °C. After 5 min the solution of ester **9** (3.86 g, 27.5 mmol) in THF (25 mL) was added dropwise over 5 min and the reaction mixture stirred for 15 min. The reaction was then quenched by the addition of saturated aq NH_4Cl solution and diluted with EtOAc (250 mL). The layers were separated and the organic layer was washed with water, brine, and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to afford the crude product, which was purified by column chromatography using 30% EtOAc/hexane (v/v) as the eluent give pure keto sulfoxide **10** (3.22 g, 13 mmol) in 52% yield as a gummy oil. TLC, R_f (40% EtOAc/hexane) 0.3. $[\alpha]_D^{25}$ −53.0 (*c* 3.0, $CHCl_3$); ν_{max} (KBr) 2924, 2854, 1631, 1040, 810 cm^{-1}; δ_H (400 MHz, $CDCl_3$): 7.51 (d, *J*=8.8 Hz, 2H), 7.30 (d, *J*=8.8 Hz, 2H), 7.09

(dd, J=15.4, 9.6 Hz, 1H), 6.27–6.03 (m, 3H), 4.02 (d, J=12.5 Hz, 1H), 3.83 (d, J=12.5 Hz, 1H), 2.42 (s, 3H), 1.90 (d, J=5.1 Hz, 3H); δ_C (75 MHz, $CDCl_3$): 190.8, 146.3, 143.0, 142.1, 139.2, 130.1, 130.0, 127.2, 124.2, 66.9, 21.4, 18.9; m/z (MS-ESI) 271 $[M+Na]^+$; HRMS (ESI) calcd for $C_{14}H_{16}O_2SNa$: 271.0768. Found: 271.0768.

*4.1.2. (2S,3E,5E)-1-(p-Tolylsulfinyl)hepta-3,5-dien-2-ol [**7**].* To a solution of anhydrous $ZnCl_2$ (2.92 g, 40 mmol) in anhydrous THF (150 mL) was added a solution of keto sulfoxide **10** (4.96 g, 20 mmol) in THF (50 mL) dropwise over 5 min. The reaction mixture was stirred at rt for 30 min and then cooled to −78 °C. After 5 min Dibal-H (21.4 mL, 1.4 M in toluene, 30 mmol) was added dropwise over 5 min. After 30 min, MeOH (5 mL) was added slowly to the reaction mixture and allowed to warm to rt. The volatiles were evaporated under reduced pressure and the residue was dissolved by adding aq 5% HCl (100 mL) at 0 °C. Then EtOAc (100 mL) was added, the layers were separated and the aqueous layer extracted with EtOAc (2×100 mL). The combined organic layers were washed with water, brine and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to afford the crude product, which was purified by column chromatography using 40% EtOAc/hexane as the eluent to give pure hydroxy sulfoxide **7** (4.1 g, 16.4 mmol) in 82% yield as a gummy oil. TLC, R_f 0.25 (40% EtOAc/hexane). $[\alpha]_D^{25}$ −194.0 (c 1.02, $CHCl_3$); ν_{max} (KBr) 3417, 2925, 2856, 1727, 1085, 994, 810 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.53 (d, J=8.1 Hz, 2H), 7.31 (d, J=8.1 Hz, 2H), 6.20 (dd, J=15.1, 10.4 Hz, 1H), 5.98 (dd, 14.9, 10.4 Hz, 1H), 5.75–5.63 (m, 1H), 5.51 (dd, J=15.1, 6.4 Hz, 1H), 4.73–4.66 (m, 1H), 3.04 (dd, J=13.0, 8.9 Hz, 1H), 2.77 (dd, J=13.0, 3.6 Hz, 1H), 2.41 (s, 3H), 1.74 (d, J=6.8 Hz, 3H); δ_C (75 MHz, $CDCl_3$) 141.6, 140.7, 131.8, 130.8, 130.6, 130.0, 129.9, 124.1, 68.9, 63.1, 21.5, 18.2; m/z (MS-ESI) 273 $[M+Na]^+$. HRMS (ESI) calcd for $C_{14}H_{18}O_2SNa$: 273.0925. Found: 273.0921.

*4.1.3. tert-Butyldimethyl((2S,3E,5E)-(1Ss)-(p-tolylsulfinyl)hepta-3,5-dien-2-yloxy) silane [**11**].* To a solution of the hydroxy sulfoxide **7** (8.0 g, 32 mmol) in DCM (128 mL) cooled at 0 °C was added imidazole (5.2 g, 76.8 mmol) and then TBS-Cl (5.77 g, 38.4 mmol). The reaction mixture was allowed to warm to rt and stirred overnight. The reaction mixture was quenched by the addition of saturated aq NH_4Cl solution, diluted with DCM (100 mL). The layers were separated and the organic layer was washed with water, brine and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to afford the crude product, which was purified by column chromatography using 10% EtOAc/hexane (v/v) as the eluent to give pure TBS ether **11** (10.48 g, 28.8 mmol) in 90% yield as a gummy oil. TLC, R_f 0.5 (20% EtOAc/hexane). $[\alpha]_D^{25}$ −41.5 (c 1.05, MeOH); 2929, ν_{max} (KBr) 2368, 1466, 1253, 1046, 990, 836, 776 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.50 (d, J=8.3 Hz, 2H), 7.30 (d, J=8.3 Hz, 2H), 6.21 (dd, J=15.1, 10.4 Hz, 1H), 6.05 (dd, 15.1, 10.6 Hz, 1H), 5.79–5.68 (m, 1H), 5.59 (dd, J=15.1, 6.4 Hz, 1H), 4.52–4.46 (m, 1H), 3.07 (dd, J=12.8, 5.3 Hz, 1H), 2.72 (dd, J=12.8, 8.3 Hz, 1H), 2.43 (s, 3H), 1.80 (d, J=6.8 Hz, 3H), 0.88 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H); δ_C (75 MHz, $CDCl_3$) 141.4, 141.3, 132.3, 131.0, 130.4, 129.9, 124.1, 69.4, 66.7, 25.7, 21.3, 18.1, −4.1, −4.9; m/z (MS-ESI) 387 $[M+Na]^+$. HRMS (ESI) calcd for $C_{20}H_{32}O_2SiSNa$: 387.1790. Found: 387.1780.

*4.1.4. (4S,5S,6R,E)-5-Bromo-6-(tert-butyldimethylsilyloxy)-(7Rs)-(p-tolylsulfinyl) hept-2-en-4-ol [**12**].* To a solution of the TBS ether **11** (4.36 g, 12 mmol) in toluene (60 mL) was added water (0.32 mL, 17.7 mmol) and the mixture stirred at rt for 5 min. To the above solution freshly recrystallised NBS (2.03 g, 11.4 mmol) was added portionwise over a period of 2 h. TLC examination revealed consumption of most of the starting material. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography using 15% EtOAc/hexane (v/v) as the eluent to give pure bromohydrin **12**(4.2 g, 9.12 mmol) in 76% yield as a gummy oil. TLC, R_f 0.25 (20% EtOAc/hexane). $[\alpha]_D^{25}$ +66.8 (c 0.5, MeOH); ν_{max} (KBr) 3360, 2928, 2856, 1631, 1255, 1085, 776 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.51 (d, J=8.3 Hz, 2H), 7.31 (d, J=8.3 Hz, 2H), 5.81–5.67 (m, 1H), 5.56 (ddd, J=16.1, 7.5, 1.5 Hz, 1H), 4.69 (dt, J=9.0, 1.5 Hz, 1H), 4.23 (br s, 1H), 4.10 (dd, J=7.5, 2.3 Hz, 1H), 3.99 (dd, J=9.0, 2.3 Hz, 1H), 3.10 (dd, J=12.8, 1.5 Hz, 1H), 2.86 (dd, J=12.8, 9.8 Hz, 1H), 2.45 (s, 3H), 1.76 (d, J=6.0 Hz, 3H), 0.99 (s, 9H), 0.28 (s, 3H), 0.22 (s, 3H); δ_C (75 MHz, $CDCl_3$) 141.5, 140.7, 130.5, 129.9, 123.9, 73.5, 66.2, 64.8, 64.1, 25.7, 21.3, 18.0, 17.6, −4.5; m/z (MS-ESI) 483 $[M+Na]^+$. HRMS (ESI) calcd for $C_{20}H_{33}O_3NaSiSBr$: 483.1000. Found: 483.0999.

*4.1.5. (4S,5S,6R)-5-Bromo-2,2-dimethyl-4-((E)-prop-1-enyl)-(6Rs)-(p-tolylsulfinylmethyl)-1,3-dioxane [**13**].* To a solution of the bromohydrin **12** (230 mg, 0.5 mmol) in THF (2 mL) were added a premixed solution of TBAF (1.5 mL, 1 M/THF, 1.5 mmol) and acetic acid (0.08 mL, 1.5 mmol) and the reaction mixture was stirred at rt for 12 h. The reaction was quenched by adding saturated aq $NaHCO_3$ (2 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with water, brine, and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to afford the crude diol as a gummy oil which was taken ahead to the next step without purification. To the crude diol in DCM (5 mL) was added 2,2-dimethoxypropane (0.18 mL, 1.5 mmol) and catalytic camphor sulfonic acid. The reaction mixture was stirred for 4 h. The solvent was evaporated under reduced pressure to afford the crude product, which was purified by column chromatography using 10% EtOAc/petroleum ether (v/v) as the eluent to give the pure product **13** (135 mg, 0.35 mmol) in 70% yield as a gummy oil. TLC, R_f 0.5 (15% EtOAc/hexane). $[\alpha]_D^{25}$ +86.8 (c 0.5, MeOH); ν_{max} (KBr) 2923, 2854, 1740, 1459, 785 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.54 (d, J=8.0 Hz, 2H), 7.30 (d, J=8.0 Hz, 2H), 5.89–5.81 (m, 1H), 5.39 (ddq, J=15.4, 7.3, 1.5 Hz, 1H), 4.51 (td, J=10.3, 1.5 Hz, 1H), 4.35 (dd, J=9.5, 7.3 Hz, 1H), 3.41–3.34 (m, 2H), 2.65 (dd, J=13.2, 10.3 Hz, 1H), 2.39 (s, 3H), 1.71 (dd, J=6.6, 1.5 Hz, 3H), 1.61 (s, 3H), 1.46 (s, 3H); δ_C (75 MHz, $CDCl_3$) 141.5, 141.2132.0, 129.9, 127.7, 123.8, 100.1, 75.3, 68.7, 62.4, 51.3, 29.3, 21.3, 19.4, 17.7. m/z (MS-ESI) 409 $[M+Na]^+$. HRMS (ESI) calcd for $C_{17}H_{23}O_3BrSNa$: 409.0448. Found: 409.0434.

*4.1.6. (5R,6S,7S,10S,11S,12R,E)-6,11-Dibromo-2,2,3,3,14,14,15,15-octamethyl-5(Rs),12(Rs)-bis(p-tolylsulfinylmethyl)-4,13-dioxa-3,14-disilahexadec-8-ene-7,10-diol [**15**].* To a solution of bromohydrin **12** (3.29 g, 7.15 mmol) in DCM (35 mL) was added Hoveyda–Grubbs catalyst **14** (90 mg, 0.143 mmol) and the reaction mixture was refluxed for 2 days. To this a second portion of the catalyst (45 mg, 0.071 mmol) was added and the reaction was continued for another 2 days when TLC revealed 80% conversion. The solvent was evaporated and the residue was purified by column chromatography using 40% EtOAc/hexane (v/v) as the eluent to give pure **15** (2.5 g, 2.86 mmol) and recovered starting material **12** (552 mg, 1.2 mmol) in 95% yield (based on recovered starting material) as a gummy oil. TLC, R_f 0.25 (50% EtOAc/hexane). $[\alpha]_D^{25}$ +105.1 (c 1.17, MeOH); ν_{max} (KBr) 3353, 2929, 2856, 1725, 1255, 1088, 676, 514 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.43 (d, J=7.9 Hz, 4H), 7.20 (d, J=7.9 Hz, 4H), 5.90–5.76 (m, 2H), 4.56 (d, J=9.8 Hz, 2H), 4.19–4.09 (m, 2H), 4.01–3.97 (m, 2H), 3.04 (dd, J=12.6, 2.5 Hz, 2H), 2.74 (dd, J=12.6, 10.0 Hz, 2H), 2.33 (s, 6H), 0.88 (s, 18H), 0.15 (s, 6H), 0.09 (s, 6H); δ_C (75 MHz, $CDCl_3$) 141.5, 140.5, 132.5, 130.0, 123.9, 72.4, 66.0, 63.9, 63.7, 25.8, 21.2, 18.0, −4.5, −4.6; m/z (MS-ESI) 889 $[M+Na]^+$. HRMS (ESI) calcd for $C_{36}H_{58}O_6\ NaS_2Si_2Br_2$: 887.1477. Found: 887.1462.

*4.1.7. (5R,6S,7S,10S,11S,12R)-6,11-Dibromo-2,2,3,3,14,14,15,15-octamethyl-5(Rs),12(Rs)-bis(p-tolylsulfinylmethyl)-4,13-dioxa-3,14-disilahexadecane-7,10-diol [**16**].* To a solution of the cross metathesis product **15** (2.5 g, 2.86 mmol) in MeOH/benzene (1:1, 28 mL)

was added Adams catalyst (100 mg) and the reaction mixture was stirred at rt under hydrogen pressure (10 bar) for 24 h. The reaction mixture was filtered through a pad of Celite and washed with MeOH. Volatiles were evaporated and the residue was purified by column chromatography using 40% EtOAc/hexane (v/v) as the eluent to give the pure reduced product **16** (1.98 g, 2.23 mmol) in 80% yield as a gummy oil. TLC, R_f 0.30 (50% EtOAc/hexane). $[\alpha]_D^{25}$ +83.0 (*c* 2.5, $CHCl_3$); ν_{max} (KBr) 3427, 1714, 1309, 1147, 814, 639 cm^{-1}; δ_H 7.52 (d, *J*=7.7 Hz, 4H), 7.32 (d, *J*=7.7 Hz, 4H), 4.74 (td, *J*=8.6, 1.9 Hz, 2H), 3.99 (dd, *J*=8.6, 2.9 Hz, 2H), 3.68 (t, *J*=8.6 Hz, 2H), 3.12 (dd, *J*=13.4, 1.9 Hz, 2H), 2.86 (dd, *J*=13.4, 8.6 Hz, 2H), 2.41 (s, 3H), 2.17–2.12 (m, 2H), 1.71–1.61 (m, 2H), 0.96 (s, 18H), 0.24 (s, 6H), 0.18 (s, 6H); δ_C (75 MHz, $CDCl_3$) 141.6, 140.3, 130.1, 123.9, 72.1, 66.3, 64.7, 63.8, 30.9, 25.7, 21.4, 18.0, −4.5, −4.6; *m*/*z* (MS-ESI) 891 $[M+Na]^+$. HRMS (ESI) calcd for $C_{36}H_{60}O_6NaS_2Si_2Br_2$: 889.1634. Found: 889.1652.

*4.1.8. (5R,6S,7S,10S,11S,12R)-6,11-Dibromo-2,2,3,3,14,14,15,15-octamethyl-5,12-bis(tosylmethyl)-4,13-dioxa-3,14-disilahexadecane-7,10-diol [**17**].* To a solution of the compound **16** (3.0 g, 3.45 mmol) in DCM (17 mL) was added *m*-CPBA (1.43 g, 8.3 mmol) at 0 °C. After 20 min the reaction was quenched by adding 10% aq $NaHSO_3$ (20 mL) and the mixture stirred for 5 min. The reaction mixture was diluted by adding DCM (20 mL). The organic layer was separated, washed with saturated $NaHCO_3$ (20 mL), water, brine, and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to afford the crude product, which was purified by column chromatography using 20% EtOAc/hexane (v/v) as the eluent to give the sulfone **17** (2.48 g, 2.76 mmol) in 80% yield as a gummy oil. TLC, R_f 0.5 (40% EtOAc/hexane). $[\alpha]_D^{25}$ +4.4 (*c* 1.25, $CHCl_3$); ν_{max} (KBr) 3427, 1714, 1309, 1147, 814, 639 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.80 (d, *J*=8.1 Hz, 4H), 7.37 (d, *J*=8.1 Hz, 4H), 4.74 (ddd, *J*=6.7, 4.4, 2.2 Hz, 2H), 4.0 (dd, *J*=9.5, 2.2 Hz, 2H), 3.81–3.71 (m, 4H), 3.24 (dd, *J*=15.4, 4.4 Hz, 2H), 2.45 (s, 6H), 2.19–2.11 (m, 2H), 1.73–1.59 (m, 2H), 0.83 (s, 18H), 0.11 (s, 6H), 0.01 (s, 6H); δ_C (75 MHz, $CDCl_3$) 145.1, 136.4, 130.1, 127.9, 72.2, 67.1, 63.2, 62.0, 30.5, 25.6, 21.6, 17.8, −4.8, −4.9; *m*/*z* (MS-ESI) 923 $[M+Na]^+$. HRMS (ESI) calcd for $C_{36}H_{60}O_8NaS_2Si_2Br_2$: 921.1532. Found: 921.1511.

*4.1.9. (5R,6S,7S,10S,11S,12R)-7,10-Bis(benzyloxy)-6,11-dibromo-2,2,3,3,14,14,15,15-octamethyl-5,12-bis(tosylmethyl)-4,13-dioxa-3,14-disilahexadecane [**18**].* To a solution of sulfone **17** (2.48 g, 3.45 mmol) and benzyl trichloroacetimidate (8.71 g, 34.5 mmol) in DCM/cyclohexane (1:1, 17 mL) was added triflic acid (0.03 mL, 0.35 mmol) dropwise at 0 °C and the reaction mixture was stirred at rt overnight. The reaction was quenched by adding aq saturated $NaHCO_3$ (2 mL). The reaction mixture was filtered through a pad of Celite and washed with DCM/cyclohexane (1:1, 30 mL). The combined organic layers were washed with water, brine and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to afford the crude product, which was purified by column chromatography using 15% EtOAc/hexane (v/v) as the eluent to give the benzyl ether **18** (2.60 g, 2.41 mmol) in 70% yield as a gummy oil. TLC, R_f 0.25 (20% EtOAc/hexane). $[\alpha]_D^{25}$ +37.3 (*c* 0.8, $CHCl_3$); ν_{max} (KBr) 2925, 2855, 1456, 1068, 924, 737 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.86 (dd, *J*=8.3 Hz, 4H), 7.53–7.38 (m, 14H), 4.93 (td, *J*=5.3, 1.7 Hz, 2H), 4.73–4.63 (m, 4H), 4.31 (dd, *J*=9.3, 1.9 Hz, 2H), 3.97–3.80 (m, 4H), 3.39 (dd, *J*=14.2, 4.9 Hz, 2H), 2.60 (s, 6H), 2.12–1.97 (m, 4H), 1.07 (s, 18H), 0.29 (s, 6H), 0.25 (s, 6H); δ_C (75 MHz, $CDCl_3$) 144.3, 137.8, 137.7, 129.9, 128.5, 128.0, 127.9, 78.6, 72.2, 68.7, 62.1, 58.9, 29.8, 26.0, 21.7, 18.2, −4.4, −4.5; *m*/*z* (MS-ESI) 1103 $[M+Na]^+$. HRMS (ESI) calcd for $C_{50}H_{72}O_8NaS_2Si_2Br_2$: 1101.2471. Found: 1101.2476.

*4.1.10. (1E,3S,4S,7S,8S,9E)-4,7-Bis(benzyloxy)-1,10-ditosyldeca-1,9-diene-3,8-diol [**21**].* To a solution of the benzyl ether **18** (2.85 g, 2.42 mmol) in THF (25 mL) was added TBAF (9.7 mL, 1 M in THF) at 0 °C dropwise over 5 min. The reaction mixture was allowed to warm to rt and stirred further for 30 min. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography using 40% EtOAc/hexane (v/v) as the eluent to give the vinyl sulfone **21** (1.20 g, 1.74 mmol) in 72% yield as a gummy oil. TLC, R_f 0.2 (40% EtOAc/hexane). $[\alpha]_D^{25}$ −24.2 (*c* 0.8, MeOH); ν_{max} (KBr) 3444, 2925, 2855, 1456, 1068, 924, 737 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.67 (d, *J*=8.3 Hz, 4H), 7.27–7.14 (m, 14H), 6.86 (dd, *J*=15.1, 3.4 Hz, 2H), 6.57 (dd, *J*=15.1, 1.9 Hz, 2H), 4.43–4.35 (m, 4H), 4.22–4.17 (m, 2H), 3.31–3.27 (m, 2H), 2.35 (s, 6H), 1.61–1.46 (m, 4H); δ_C (75 MHz, $CDCl_3$) 144.8, 144.3, 137.4, 137.3, 131.8, 129.9, 128.7, 128.2, 128.1, 127.8, 80.3, 72.9, 71.5, 26.4, 21.7; *m*/*z* (MS-ESI) 713 $[M+Na]^+$. HRMS (ESI) calcd for $C_{38}H_{42}O_8NaS_2$: 713.2218. Found: 713.2238.

*4.1.11. (3S,4S,7S,8S)-4,7-Bis(benzyloxy)deca-1,9-diene-3,8-diol [**6**].* To a solution of vinyl sulfone **21** (1.20 g, 1.74 mmol) in ethanol (17 mL) was added magnesium turnings (250 mg, 10.44 mmol) followed by $HgCl_2$ (few crystals) at 0 °C. The reaction mixture was stirred for 4 h, while gradually allowing the temperature to rise to rt. The residue was filtered and washed with ethanol. The combined filtrates were concentrated under reduced pressure to afford the crude product, which was purified by column chromatography using 15% EtOAc/hexane (v/v) as the eluent to afford the diol **6** (0.47 g, 1.22 mmol) in 70% yield as a gummy oil. TLC, R_f 0.3 (20% EtOAc/hexane). $[\alpha]_D^{25}$ −35.8 (*c* 0.6, MeOH); ν_{max} (KBr) 3427, 2922, 2856, 1639, 1452, 1065, 923, 698 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.32–7.28 (m, 10H), 5.85 (ddd, *J*=17.4, 10.6, 6.0 Hz 2H), 5.33 (dt, *J*=17.4, 1.5 Hz, 2H), 5.21–5.20 (dt, *J*=10.6, 1.5 Hz, 2H), 4.59 (d, *J*=11.3 Hz, 2H), 4.53 (d, *J*=11.3 Hz, 2H), 4.05 (t, *J*=6.0 Hz, 2H), 3.34 (dt, *J*=10.6, 6.0 Hz, 2H), 1.75–1.56 (m, 4H); δ_C NMR (75 MHz, $CDCl_3$) 138.1, 137.3, 128.5, 127.8, 117.0, 81.9, 74.2, 72.5, 25.4; *m*/*z* (MS-ESI) 405 $[M+Na]^+$. HRMS (ESI) calcd for $C_{24}H_{30}O_4Na$: 405.2041. Found: 405.2052.

*4.1.12. (E)-Ethyl tridec-2-enoate [**23**].* To a solution of 1-undecanal **22** (3.4 g, 20 mmol) in benzene (80 mL) was added ethyl-(triphenylphosphoranylidene)acetate (8.35 g, 24 mmol) and the reaction mixture was heated to reflux for 15 h. The reaction mixture was cooled to rt and benzene was evaporated under reduced pressure. The residue was cooled to 0 °C diluted with ether and the mixture filtered through a sintered funnel to remove the triphenylphosphineoxide. The ether layer was evaporated under reduced pressure to afford the crude product, which was purified by column chromatography using 5% EtOAc/hexane (v/v) as the eluent to give **23** (3.84 g, 16.0 mmol) in 80% yield as a colorless liquid. TLC, R_f 0.5 (5% EtOAc/hexane). ν_{max} (KBr) 2926, 2855, 1723, 1181, 1042 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 6.89 (dt, *J*=15.5, 7.0 Hz, 1H), 5.75 (d, *J*=15.5 Hz, 1H), 4.14 (q, *J*=7.2 Hz, 2H), 2.17 (q, *J*=7.0 Hz, 2H), 1.45–1.19 (m, 19H), 0.86 (t, *J*=6.8 Hz, 3H); δ_C (75 MHz, $CDCl_3$) 166.5, 149.2, 121.3, 60.0, 32.2, 31.9, 29.6, 29.5, 29.4, 29.3, 29.2, 28.1, 22.7, 14.3, 14.1; *m*/*z* (MS-ESI) 263 $[M+Na]^+$. HRMS (ESI) calcd for $C_{15}H_{28}O_2Na$: 263.1987. Found: 263.1994.

*4.1.13. (E)-Tridec-2-en-1-ol [**24**].* To a suspension of $LiAlH_4$ (570 mg, 15 mmol) in ether (12 mL) cooled at 0 °C was added a solution of $AlCl_3$ (670 mg, 5 mmol) in ether (8 mL). The reaction mixture was stirred at the same temperature for 1 h. To the alane so generated, a solution of the ester **23** (2.4 g, 10 mmol) in ether (15 mL) was added dropwise over 2 min. The reaction temperature was gradually allowed to rise to rt and the reaction mixture stirred for 2 h. The reaction mixture was diluted with ether (30 mL), and quenched by careful addition of ice pieces until the reaction ceased. The reaction mass was filtered through a pad of Celite and washed with hot ethyl acetate. The combined organic layers were washed with water, brine, and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to afford the crude product, which was purified

by column chromatography using 15% EtOAc/hexane (v/v) as the eluent to afford the pure compound **24** (1.49 g, 7.5 mmol) in 75% yield as a colorless liquid. TLC: R_f 0.2 (20% EtOAc/hexane). ν_{max} (KBr) 3329, 2924, 2853, 1631, 1461, 1089, 969 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 5.65–5.51 (m, 2H), 4.67 (br s, 1H), 4.05 (d, J=3.9 Hz, 2H), 2.04 (q, J=6.3 Hz, 2H), 1.56–1.07 (m, 16H), 0.88 (t, J=7.0 Hz, 3H); δ_C NMR (75 MHz, $CDCl_3$) 136.6, 123.9, 65.3, 32.4, 32.0, 29.7, 29.6, 29.4, 29.3, 29.0, 22.8, 14.2. m/z (MS-ESI) 221 $[M+Na]^+$. HRMS (ESI) calcd for $C_{13}H_{26}ONa$: 221.1881. Found: 221.1886.

*4.1.14. ((2R,3R)-3-Decyloxiran-2-yl)methanol [**25**].* To a stirred suspension of activated 4 Å molecular sieves (660 mg) in DCM (28 mL) was added (−)DET (0.34 mL, 2 mmol) and $Ti(O^iPr)_4$ (0.6 mL, 2 mmol) and the resulting mixture was stirred for 30 min at rt. The reaction mixture was then cooled to −20 °C and a solution of the allylic alcohol **24** (1.98 g, 10 mmol) in DCM (4 mL) was added dropwise into it. The resulting mixture was stirred for another 30 min at −20 °C. TBHP (6.1 mL, 3.6 M in toluene, 22 mmol) was added dropwise and the resulting mixture stirred at the same temperature for 12 h. The reaction mixture was allowed to warm to 0 °C, quenched with water (11.2 mL) and stirred for 2 h at rt. Then aq NaOH (30%) saturated with NaCl (4 mL) was added and the resulting mixture was stirred vigorously for another 30 min at rt. The mixture was filtered through Celite and the filter cake was washed well with DCM. The organic layers were separated and the aqueous layer was extracted with DCM (3×25 mL). The combined extracts were washed with water, brine and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to afford the crude product, which was purified by column chromatography using 20% EtOAc/hexane (v/v) as the eluent to give the pure product **25** (1.71 g, 8.0 mmol) in 80% yield as a gummy solid. TLC, R_f 0.2 (30% EtOAc/hexane). $[\alpha]_D^{25}$ +47.3 (c 3.0, $CHCl_3$); ν_{max} (KBr) 3287, 2923, 2852, 1460, 1250, 872, 719 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 3.87 (ddd, J=12.5, 5.5, 2.3 Hz, 1H), 3.59 (ddd, J=12.5, 7.8, 3.9 Hz, 1H), 2.94–2.83 (m, 2H), 1.60–1.23 (m, 18H), 0.90 (t, J=6.2 Hz, 3H); δ_C (75 MHz, $CDCl_3$) 61.7, 58.4, 56.0, 31.8, 31.5, 29.5, 29.4, 29.3, 25.9, 22.6, 14.0; m/z (MS-ESI) 215 $[M+H]^+$. HRMS (ESI) calcd for $C_{13}H_{26}O_2Na$: 237.1830. Found: 237.1835.

*4.1.15. ((2R,3R)-3-Decyloxiran-2-yl)methyl 4-methylbenzenesulfonate [**5**].* To a solution of the epoxy alcohol **25** (1.71 g, 8.0 mmol) in DCM (40 mL) were added Et_3N (2.24 mL, 16 mmol) and catalytic amounts of DMAP. The reaction mixture was cooled to 0 °C and tosyl chloride (1.85 g, 9.6 mmol) was added. The reaction was stirred gradually allowing the temperature to rise to rt for 3 h. The reaction mixture was diluted with DCM (50 mL). The organic layer was washed with water, brine, and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to afford the crude product, which was purified by column chromatography using 10% EtOAc/hexane (v/v) as the eluent to give the pure tosylate **5** (2.65 g, 7.2 mmol) in 90% yield as a gummy solid. TLC, R_f 0.2 (10% EtOAc/hexane). $[\alpha]_D^{25}$ +37.3 (c 2.0, $CHCl_3$); ν_{max} (KBr) 3445, 2920, 2850, 1640, 1250, 870, 570 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.78 (d, J=8.3 Hz, 2H), 7.33 (d, J=8.3 Hz, 2H), 4.10 (dd, J=11.3, 4.5 Hz, 1H), 3.95 (dd, J=11.3, 6.0 Hz, 1H), 2.90–2.87 (m, 1H), 2.75–2.71 (m, 1H), 2.46 (s, 3H), 1.55–1.20 (m, 18H), 0.89 (t, J=6.8 Hz, 3H); δ_C (75 MHz, $CDCl_3$) 144.5, 133.5, 129.8, 128.1, 69.9, 56.7, 54.4, 31.9, 31.4, 29.7, 29.6, 29.5, 29.4, 25.8, 22.7, 21.7, 14.3; m/z (MS-ESI) 391 $[M+Na]^+$. HRMS (ESI) calcd for $C_{20}H_{32}O_4SNa$: 391.1919. Found: 391.1916.

*4.1.16. (2R,3S)-3-((3S,4S,7S,8S)-4,7-Bis(benzyloxy)-8-hydroxydeca-1,9-dien-3-yloxy)-2-hydroxytridecyl 4-methylbenzenesulfonate [**26**].* To a solution of the mixture of diol **6** (1.14 g, 3 mmol), epoxy tosylate **5** (1.32 g, 3.6 mmol) and activated powdered 4 Å MS (100 mg) in DCM (6.6 mL) cooled at 0 °C was added freshly distilled $BF_3\cdot Et_2O$ (38 μL, 0.3 mmol). The reaction mixture was allowed to gradually warm to rt and stirred further for 24 h. The reaction mixture was recooled to 0 °C and another portion of $BF_3\cdot Et_2O$ (19 μL, 0.15 mmol) was added and stirring continued for another 15 h at rt. The reaction was quenched by adding few pieces of ice and the mixture was stirred for 10 min. The reaction mixture was filtered through a pad of Celite and the residue was washed with DCM. The organic layer was washed with water, brine and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to afford the crude product, which was purified by column chromatography using 15% EtOAc/hexane (v/v) as the eluent to give pure product **26** (1.58 g, 2.1 mmol) in 70% yield as a gummy oil. TLC, R_f 0.25 (20% EtOAc/hexane). $[\alpha]_D^{25}$ −19.0 (c 1.0, MeOH); ν_{max} (KBr) 3445, 2923, 2855, 1725, 1457, 1074, 742 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.77 (d, J=8.5 Hz, 2H), 7.36–7.24 (m, 12H), 5.88–5.74 (m, 1H), 5.67–5.56 (m, 1H), 5.35–5.17 (m, 4H), 4.65–4.47 (m, 4H), 4.19–3.98 (m, 3H), 3.90–3.74 (m, 2H), 3.43 (dd, J=6.9, 5.3 Hz, 1H), 3.30 (m, 2H), 2.43 (s, 3H), 1.72–1.17 (m, 22H), 0.88 (t, J=6.4 Hz, 3H); δ_C (75 MHz, $CDCl_3$) 144.9, 138.5, 138.1, 137.4, 135.1, 129.8, 128.4, 128.3, 127.9, 127.8, 127.7, 127.6, 119.7, 116.7, 81.7, 81.6, 80.7, 76.4, 74.0, 73.1, 72.3, 71.3, 70.5, 31.9, 29.8, 29.6, 29.5, 29.3, 25.9, 25.8, 24.5, 22.6, 21.6, 14.1; m/z (MS-ESI) 768 $[M+NH_4]^+$, 773 $[M+Na]^+$. HRMS (ESI) calcd for $C_{44}H_{62}O_8NaS$: 773.4063. Found: 773.4089.

*4.1.17. (3S,4S,7S,8S)-4,7-Bis(benzyloxy)-8-((S)-1-((R)-oxiran-2-yl) undecyloxy)deca-1,9-dien-3-ol [**27**].* To a solution of the tosylate **26** (1.58 g, 2.1 mmol) in a mixture of acetonitrile/ethanol (1:1, 20 mL) was added anhydrous K_2CO_3 (1.18 g, 4.4 mmol) and the reaction mixture was stirred at rt for 12 h. The reaction mixture was passed through a pad of Celite and the Celite pad was washed with acetonitrile (15 mL). The combined organic layers were evaporated under reduced pressure to afford the crude product, which was purified by column chromatography using 10% EtOAc/hexane (v/v) as the eluent to give the epoxide **27** (1.09 g, 1.89 mmol) in 90% yield as a gummy oil. TLC, R_f 0.3 (20% EtOAc/hexane). $[\alpha]_D^{25}$ −17.2 (c 2.52, MeOH); ν_{max} (KBr) 3432, 2924, 2854, 1763, 1457, 1243, 1058, 923, 699 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.33–7.17 (m, 10H), 5.83–5.66 (m, 2H), 5.31–5.11 (m, 4H), 4.74–4.42 (m, 4H), 3.97 (t, J=5.5 Hz, 1H), 3.81 (t, J=6.6 Hz, 1H), 3.34–3.21 (m, 2H), 3.08 (dd, J=11.3, 5.5 Hz, 1H), 2.77–2.72 (m, 1H), 2.63 (dd, J=5.5, 4.0 Hz, 1H), 2.50 (dd, J=5.3, 2.6 Hz, 1H), 1.66–1.14 (m, 22H), 0.85 (t, J=6.0 Hz, 3H); δ_C (75 MHz, $CDCl_3$) 138.7, 138.2, 137.7, 136.4, 128.4, 128.3, 127.8, 127.7, 127.6, 127.5, 117.7, 116.4, 82.0, 81.9, 80.9, 77.8, 73.9, 73.0, 72.3, 53.4, 46.1, 32.9, 32.0, 30.0, 29.7, 29.6, 29.5, 29.4, 26.0, 25.8, 25.0, 22.7, 14.2; m/z (MS-ESI) 601 $[M+Na]^+$. HRMS (ESI) calcd for $C_{37}H_{54}O_5Na$: 601.3868. Found: 601.3858.

*4.1.18. (3R,4S)-4-((3S,4S,7S,8S)-4,7-Bis(benzyloxy)-8-hydroxydeca-1,9-dien-3-yloxy)tetradec-1-en-3-ol [**4**].* To a suspension of trimethylsulfonium iodide (184 mg, 0.9 mmol) in anhydrous THF (2.8 mL) cooled at −10 °C was added n-BuLi (0.3 mL, 2.4 M in hexanes, 0.72 mmol) and the reaction mixture stirred for 1 h. To this a solution of the epoxide **27** (110 mg, 0.18 mmol) in THF (1.8 mL) was added dropwise. The reaction mixture was gradually allowed to warm to rt and stirred for 4 h. The reaction was quenched by adding saturated aq NH_4Cl, it was then filtered through a pad of Celite and the residue was washed with EtOAc. The combined organic layers were washed with water, brine and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to afford the crude product, which was purified by column chromatography using 15% EtOAc/hexane (v/v) as the eluent to give pure **4** (79 mg, 0.13 mmol) in 70% yield as a gummy oil. TLC: R_f 0.3 (30% EtOAc/hexane). $[\alpha]_D^{25}$ −37.3 (c 1.0, MeOH); ν_{max} (KBr) 3540, 2925, 2362, 1638, 1147, 772 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.33–7.21 (m, 10H), 5.88–5.69 (m, 3H), 5.34–5.13 (m, 6H), 4.69–4.45 (m, 4H), 4.08–4.05 (m, 1H), 4.00 (t, J=5.9 Hz, 1H), 3.90 (t, J=6.0 Hz, 1H), 3.41–3.33 (m, 2H), 3.27 (dd, J=10.6, 4.7 Hz, 1H), 1.70–1.18 (m, 22H),

0.9 (t, J=6.6 Hz, 3H), m/z (MS-ESI) 615 $[M+Na]^+$. HRMS (ESI) calcd for $C_{38}H_{56}O_5Na$: 615.4025. Found: 615.4035.

*4.1.19. (2S,3R,6S)-6-((1S,4S,5S)-1,4-Bis(benzyloxy)-5-hydroxyhept-6-enyl)-2-decyl-3,6-dihydro-2H-pyran-3-ol [**2**] and (1S,4S,5S,8S,Z)-5,8-bis(benzyloxy)-4-((3R,4S)-3-hydroxytetradec-1-en-4-yloxy)cyclooct-2-enol [**29**].* To a solution of the allylic alcohol **4** (79 mg, 0.13 mmol) in DCM (27 mL) was added Grubbs second generation catalyst **28** (6 mg, 0.007 mmol) and the mixture refluxed for 12 h. The solvent was evaporated under reduced pressure to afford the crude product, which was purified by column chromatography using 30% EtOAc/hexane (v/v) as the eluent, the product **2** eluted initially (30 mg, 0.05 mmol) in 38% yield and the cyclooctene derivative **29** eluted next (30 mg, 0.05 mmol) in 38% yield.

Compound **2**: Gummy oil. TLC, R_f 0.2 (30% EtOAc/hexane). $[\alpha]_D^{25}$ −72.0 (c 2.0, MeOH); ν_{max} (KBr) 3428, 2923, 2855, 1455, 1069, 739 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.34–7.23 (m, 10H), 5.87–5.75 (m, 3H), 5.32 (dt, J=15.6, 1.5 Hz, 1H), 5.17 (dt, J=10.4, 1.5 Hz, 1H), 4.69–4.47 (m, 4H), 4.29–4.25 (m, 1H), 4.0 (t, J=5.8 Hz, 1H), 3.89–3.84 (m, 1H), 3.45–3.37 (m, 1H), 3.28 (dd, J=10.6, 5.9 Hz, 1H), 3.14 (dt, J=8.3, 2.6 Hz, 1H), 1.68–1.20 (m, 22H), 0.89 (t, J=7.0 Hz, 3H). m/z (MS-ESI) 587 $[M+Na]^+$. HRMS (ESI) calcd for $C_{36}H_{52}O_5Na$: 587.3712 Found: 587.3733.

Compound **29**: Gummy oil. TLC, R_f 0.1 (30% EtOAc/hexane). $[\alpha]_D^{25}$ −82.0 (c 2.2, MeOH); ν_{max} (KBr) 3422, 2920, 2850, 1440, 1071, 739 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.35–7.22 (m, 10H), 6.13–6.07 (m, 1H), 5.87–5.78 (m, 2H), 5.3 (dt, J=15.2, 1.5 Hz, 1H), 5.2 (dt, J=10.5, 1.5 Hz, 1H), 4.63–4.46 (m, 4H), 4.16–4.11 (m, 1H), 4.04 (t, J=5.5 Hz, 1H), 3.90 (td, J=8.7, 2.6 Hz, 1H), 3.73–3.69 (m, 1H), 3.42 (dd, J=10.6, 5.9 Hz, 1H), 3.32 (t, J=5.9 Hz, 1H), 2.3 (dd, J=14.6, 7.9 Hz, 1H), 2.07–1.96 (m, 1H), 1.71–1.08 (m, 20H), 0.88 (t, J=6.8 Hz, 3H). m/z (MS-ESI) 587 $[M+Na]^+$. HRMS (ESI) calcd for $C_{36}H_{52}O_5Na$: 587.3712. Found: 587.3703.

*4.1.20. ((3S,4S,7S,8S)-4,7-Bis(benzyloxy)-8-((S)-1-((R)-oxiran-2-yl) undecyloxy)deca-1,9-dien-3-yloxy)triethylsilane [**30**].* To a solution of the carbinol **27** (1.15 g, 2.0 mmol) in DCM (10 mL) cooled at 0 °C was added imidazole (0.27 g, 4 mmol) followed by TES-Cl (0.5 mL, 3 mmol) dropwise. The reaction mixture was gradually allowed to warm to rt and stirred for 2 h. The reaction was quenched by adding saturated aq NH_4Cl solution. The organic layer was separated and the aqueous layer was extracted with DCM. The combined organic layers were washed with water, brine and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to afford the crude product, which was purified by column chromatography using 10% EtOAc/hexane (v/v) as the eluent to give the product **30** (1.25 g, 1.8 mmol) in 90% yield as the gummy oil. TLC, R_f 0.5 (15% EtOAc/hexane). $[\alpha]_D^{25}$ −2.0 (c 1.0, MeOH); ν_{max} (KBr) 2925, 2859, 1727, 1458, 1078, 736 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.27–7.12 (m, 10H), 5.85–5.54 (m, 2H), 5.19–5.03 (m, 4H), 4.67–4.42 (m, 4H), 4.14 (t, J=5.5 Hz, 1H), 3.73 (t, J=6.6 Hz, 1H), 3.28–3.15 (m, 2H), 3.00 (dd, J=11.3, 6.0 Hz, 1H), 2.71–2.67 (m, 1H), 2.56 (dd, J=5.3, 3.8 Hz, 1H), 2.44 (dd, J=5.3, 2.6 Hz, 1H), 1.57–1.13 (m, 22H), 0.88–0.81 (m, 12H), 0.48 (q, J=7.9 Hz, 6H); δ_C (75 MHz, $CDCl_3$) 139.0, 138.9, 137.6, 136.6, 128.1, 127.7, 127.6, 127.4, 117.3, 115.4, 82.5, 82.3, 81.2, 78.0, 74.6, 73.0, 72.7, 53.4, 46.2, 33.0, 32.0, 30.0, 29.7, 29.6, 29.5, 29.4, 26.8, 25.8, 24.9, 22.7, 14.2, 6.9, 5.0; m/z (MS-ESI) 715 $[M+Na]^+$. HRMS (ESI) calcd for $C_{43}H_{68}O_5NaSi$: 715.4734. Found: 715.4744.

*4.1.21. (3R,4S)-4-((3S,4S,7S,8S)-4,7-Bis(benzyloxy)-8-(triethylsilyloxy)deca-1,9-dien-3-yloxy)tetradec-1-en-3-ol [**31**].* To a suspension of trimethylsulfonium iodide (1.84 g, 9 mmol) in anhydrous THF (28 mL) cooled at −10 °C was added n-BuLi (3.6 mL, 2.5 M in hexanes, 9 mmol) and the reaction mixture was stirred for 1 h. To this a solution of the epoxide **30** (1.25g, 1.8 mmol) in THF (2.5 mL) was added dropwise. The reaction mixture was gradually allowed to warm to rt and stirred for 4 h. The reaction was quenched by adding saturated aq NH_4Cl, it was then filtered through a pad of Celite and the residue was washed with EtOAc. The combined organic layers were washed with water, brine, and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to afford the crude product, which was purified by column chromatography using 15% EtOAc/hexane (v/v) as the eluent to give pure **31** (0.95g, 1.35 mmol) in 70% yield. As a gummy oil. TLC, R_f 0.2 (20% EtOAc/hexane). $[\alpha]_D^{25}$ −17.3 (c 1.0, MeOH); ν_{max} (KBr) 3452, 2934, 2862, 1739, 1451, 1070, 742 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.24–7.19 (m, 10H), 5.93–5.68 (m, 3H), 5.26–5.11 (m, 6H), 4.67–4.50 (m, 4H), 4.22 (t, J=5.5 Hz, 1H), 4.09–4.03 (m, 1H), 3.85 (dd, J=7.4, 6.2 Hz, 1H), 3.43–3.24 (m, 3H), 1.68–1.16 (m, 22H), 0.96–0.87 (m, 12H), 0.56 (q, J=7.7 Hz, 6H); δ_C (75 MHz, $CDCl_3$) 138.9, 138.8, 137.7, 136.7, 136.3, 128.2, 127.8, 127.5, 118.7, 116.2, 115.5, 82.4, 81.1, 80.3, 74.7, 74.1, 73.1, 72.7, 32.0, 30.0, 29.8, 29.7, 29.6, 29.4, 26.9, 25.8, 25.7, 22.8, 14.2, 7.0, 5.0; m/z (MS-ESI) 729 $[M+Na]^+$. HRMS (ESI) calcd for $C_{44}H_{70}O_5NaSi$: 729.4890. Found: 729.4908.

*4.1.22. (2S,3R,6S)-6-((1S,4S,5S)-1,4-Bis(benzyloxy)-5-(triethylsilyloxy)hept-6-enyl)-2-decyl-3,6-dihydro-2H-pyran-3-ol [**32**].* To a solution of the allylic alcohol **31** (0.953 g, 1.35 mmol) in DCM (270 mL) was added Grubbs second generation catalyst **28** (58 mg, 0.067 mmol) and refluxed for 12 h. The solvent was evaporated under reduced pressure to afford the crude product, which was purified by column chromatography using 20% EtOAc/hexane (v/v) as the eluent to give the pure product **32** (0.79 g, 1.16 mmol) in 85% yield as a gummy oil. TLC, R_f 0.2 (25% EtOAc/hexane). $[\alpha]_D^{25}$ −89.0 (c 2.25 MeOH); ν_{max} (KBr) 3448, 2926, 2855, 1728, 1635, 1255, 1023, 613 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.32–7.16 (m, 10H), 5.92–5.74 (m, 3H), 5.16 (dt, J=17.2, 1.7 Hz, 1H), 5.10 (dt, J=10.6, 1.7 Hz, 1H), 4.65 (d, J=8.9 Hz, 1H), 4.61 (d, J=8.9 Hz, 1H), 4.53 (d, J=5.9 Hz, 1H), 4.50 (d, J=5.9 Hz, 1H), 4.24–4.17 (m, 2H), 3.86–3.82 (m, 1H), 3.37 (dd, J=11.1, 6.0 Hz, 1H), 3.29–3.23 (m, 1H), 3.11 (td, J=8.5, 2.5 Hz, 1H), 1.78–1.20 (m, 22H), 0.96–0.86 (m, 12H), 0.55 (q, J=7.7 Hz, 6H); δ_C (75 MHz, $CDCl_3$) 138.9, 138.8, 137.8, 130.5, 128.8, 128.2, 127.9, 127.7, 127.4, 115.5, 82.3, 80.4, 79.6, 75.7, 74.8, 72.9, 72.5, 68.1, 32.5, 32.0, 29.9, 29.8, 29.7, 29.6, 26.4, 26.2, 26.0, 22.8, 14.3, 7.0, 4.9; m/z (MS-ESI) 696 $[M+NH4^+]^+$. HRMS (ESI) calcd for $C_{42}H_{66}O_5NaSi$: 701.4577. Found: 701.4567.

*4.1.23. ((2S,3R,6S)-6-((1S,4S,5S)-1,4-Bis(benzyloxy)-5-(triethylsilyloxy)hept-6-enyl)-2-decyl-3,6-dihydro-2H-pyran-3-yloxy)(tert-butyl)dimethylsilane [**33**].* To a solution of the pyran derivative **32** (0.79 g, 1.16 mmol) in DCM (12 mL) was added 2,6-lutidine (0.32 mL, 2.78 mmol) and the reaction mixture was cooled to −78 °C. TBSOTf (0.32 mL, 1.39 mmol) was added dropwise and the reaction mixture was stirred at the same temperature for 15 min. The reaction was quenched by adding saturated aq NH_4Cl solution (5 mL). The layers were separated and the layer was extracted with DCM (10 mL). The combined organic layers were washed with water, brine and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to afford the crude product, which was purified by column chromatography using 5% EtOAc/hexane (v/v) as the eluent to give the pure product **33** (0.78 g, 0.98 mmol) in 85% yield as a gummy oil. TLC, R_f 0.2 (25% EtOAc/hexane). $[\alpha]_D^{25}$ −104.0 (c 2.5, $CHCl_3$); ν_{max} (KBr) 2923, 2853, 1461, 1088, 836, 733 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.30–7.19 (m, 10H), 5.92–5.66 (m, 3H), 5.22 (dt, J=17.2, 1.3 Hz, 1H), 5.11 (dt, J=10.4, 1.3 Hz, 1H), 4.65 (d, J=8.7 Hz, 1H), 4.61 (d, J=8.7 Hz, 1H), 4.54 (d, J=9.6 Hz, 1H), 4.50 (d, J=9.6 Hz, 1H), 4.24–4.17 (m, 2H), 3.88 (dd, J=8.1, 2.6 Hz, 1H), 3.39–3.13 (m, 3H), 1.76–1.16 (m, 22H), 0.99–0.85 (m, 21 H), 0.55 (q, J=7.7 Hz, 6H), 0.08 (s, 3H), 0.06 (s, 3H). δ_C (75 MHz, $CDCl_3$) 139.0, 138.8, 137.9, 131.4, 128.2, 127.9, 127.8, 127.7, 127.4, 115.5, 82.3, 80.5, 79.1, 75.9, 74.8, 72.8, 72.5, 68.6, 32.2, 32.0, 29.7, 29.6, 29.4, 26.4, 26.2, 25.9, 25.4, 22.7, 18.1, 14.2, 7.0, 4.9,

−4.0, −4.6. *m/z* (MS-ESI) 816 $[M+Na]^+$. HRMS (ESI) calcd for $C_{48}H_{80}O_5NaSi_2$: 815.5442. Found: 815.5440.

*4.1.24. Dec-9-ynal [**35**].* To a solution of oxalyl chloride (8.2 mL, 93.45 mmol) in DCM (200 mL) cooled at −78 °C under nitrogen atmosphere was added a solution of DMSO (8.7 mL, 124.6 mmol) in DCM (15 mL) dropwise and stirred for 5 min at this temperature. To the above, a solution of the alcohol **34** (9.6 g, 62.3 mmol) in DCM (15 mL) was added dropwise. The reaction mixture was stirred for 30 min at this temperature, Et_3N (43.7 mL, 311.5 mmol) was added dropwise at −78 °C and the reaction mixture was allowed to warm to rt. Water (200 mL) was added and the organic layer was separated. The aq layer was extracted with DCM (2×100 mL). The combined organic layers were washed successively with 1 M HCl (100 mL), water, brine, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to afford the crude aldehyde which was purified by column chromatography using 10% EtOAc/hexane (v/v) as the eluent to give pure aldehyde **35** (8.52 g, 56.07 mmol) in 90% yield as a gummy oil. TLC, R_f 0.3 (15% EtOAc/hexane); ν_{max} (KBr) 2930, 1725, 1636, 769 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 9.75 (s, 1H), 2.33 (t, *J*=7.4 Hz, 2H), 2.16 (td, *J*=6.6, 2.2 Hz, 2H), 1.84 (t, *J*=2.2 Hz, 1H), 1.70–1.31 (m, 10H). δ_C (75 MHz, $CDCl_3$) 180.1, 84.5, 68.1, 33.9, 28.8, 28.6, 28.4, 28.3, 24.5, 18.2; *m/z* (MS -EI) 175 $[M+Na]^+$. HRMS (ESI) calcd for $C_{10}H_{16}ONa$: 175.1098. Found: 175.1093.

*4.1.25. (R)-Dec-9-yne-1,2-diol [**36**].* DMSO (4 mL) was added to L-proline (55.2 mg, 0.48 mmol), and DMSO (4 mL) at rt under nitrogen atmosphere and the suspension was stirred for 10 min. Nitrosobenzene (257 mg, 2.4 mmol) was added in one portion at which time the solution became green. Aldehyde **35** (400 mg, 2.63 mmol) in DMSO (11 mL) was added in one portion to the above greenish suspension and stirring continued at rt until the reaction was determined to be complete by TLC (the change of color of the green colour solution to a yellow homogeneous solution was observed). The reaction mixture was then transferred to a suspension of $NaBH_4$ (365 mg, 9.6 mmol) in ethanol (5 mL) at 0 °C. After 20 min of stirring, the reaction mixture was treated with saturated aq $NaHCO_3$ (15 mL) and extracted with dichloromethane (3×10 mL). The combined organic layers were washed with brine (15 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo to afford the crude anilinoxy compound (470 mg, 1.8 mmol) in 75% yield, which was used immediately for the next reaction. (b) To a solution of the above anilinoxy compound (470 mg, 1.8 mmol) in methanol (8 mL), was added $CuSO_4 \cdot 5H_20$ (174 mg, 0.61 mmol). The reaction mixture was stirred at rt overnight and then quenched with a cold saturated NH_4Cl solution (5 mL). The mixture was filtered on a Celite pad and washed thoroughly with ethyl acetate (15 mL). The volatiles were removed under reduced pressure. The residue was extracted with ethyl acetate (3×15 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to afford the crude product, which was purified by column chromatography using 30% EtOAc/hexane (v/v) as the eluent to give pure diol **36** (214 mg, 1.26 mmol) in 70% yield as a gummy oil. TLC, R_f 0.25 (40% EtOAc/hexane). $[\alpha]_D^{25}$ +8.6 (*c* 1.02, $CHCl_3$); ν_{max} (KBr) 3405, 2933, 2858, 1639, 1460, 1061, 770 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 4.07 (br s, 1H), 3.64–3.49 (m, 3H), 3.3 (dd, *J*=11.3, 8.3 Hz, 1H), 2.14 (td, *J*=6.8, 2.3 Hz, 2H), 1.84 (t, *J*=2.3 Hz, 1H), 1.53–1.23 (m, 10H). δ_C (75 MHz, $CDCl_3$) 84.6, 72.2, 68.2, 66.7, 33.0, 29.0, 28.5, 28.3, 25.4, 18.3. *m/z* (MS-EI) 193 $[M+Na]^+$. HRMS (ESI) calcd for $C_{10}H_{18}O_2Na$: 193.1204. Found: 193.1211.

*4.1.26. (S)-3-((R)-2-(tert-Butyldimethylsilyloxy)dec-9-ynyl)-5-methyl-3-(phenylthio)dihydrofuran-2(3H)-one [**40**].* Freshly distilled Tf_2O (0.6 mL, 3.62 mmol) was added to a mixture of diol **36** (550 mg, 3.23 mmol) and 2,6-lutidine (1.88 mL, 16.15 mmol) in DCM (30 mL) at −50 °C. After 15 min, TBSOTf (1.11 mL, 4.84 mmol) was added and the mixture was stirred for 5 min at 0 °C. The reaction was quenched by adding saturated aq NH_4Cl (10 mL) and the mixture was extracted with Et_2O. The extract was washed with saturated aq NH_4Cl, water, and brine prior to drying and solvent evaporation. The residue was purified by column chromatography using 10% EtOAc/hexane (v/v) as the eluent to give pure triflate **38** (1.24 g, 3.0 mmol) in 93% yield, which was used immediately for the next step. To a solution of LHMDS (1.0 M in THF, 6.0 mL, 6.0 mmol) in THF (15 mL) cooled at −78 °C was added lactone **39** (1.24 g, 6 mmol) in THF (18 mL). The mixture was stirred for 10 min, then at 0 °C for 10 min and again cooled to −78 °C. After 10 min of stirring, HMPA (19 mL) was added and then after 5 min, the solution of triflate **38** (1.24 g, 3.0 mmol) in THF (44 mL), precooled to −78 °C was canulated into it. After 10 min, the mixture was allowed to warm to 0 °C over a period of 15 min, then stirred at rt for 10 min and quenched with aq NH_4Cl extracted with ether (3×50 mL) and the combined organic layers were washed with saturated NH_4Cl (30 mL). The organic layer was separated and washed with brine (30 mL), dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to afford the crude product, which was purified by column chromatography using 20% EtOAc/hexane (v/v) as the eluent to give the alkylated product **40** as a diastereomeric mixture (924 mg, 1.95 mmol) in 65% yield as a gummy oil. TLC, R_f 0.25 (25% EtOAc/hexane). $[\alpha]_D^{25}$ −89.0 (*c* 2.25 MeOH); ν_{max} (KBr) 2931, 2857, 1766, 1465, 1184, 834 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.53–7.24 (m, 10H), 4.63–4.42 (m, 2H), 4.26–4.16 (m, 1H), 3.82–3.73 (m, 1H), 2.98 (dd, *J*=14.4, 7.6 Hz, 1H), 2.43 (dd, *J*=14.4, 10.6 Hz, 1H), 2.24 (*J*=14.4, 7.6 Hz, 1H), 2.16–2.06 (m, 4H), 2.0–1.76 (m, 7H), 1.56–1.09 (m, 26H), 0.88 (s, 9H), 0.85 (s, 9H), 0.14 (s, 3H), 0.10 (s, 3H), 0.01 (s, 3H), 0.00 (s, 3H). δ_C (75 MHz, $CDCl_3$) 176.7, 174.3, 137.1, 136.7, 130.5, 129.9, 129.5, 128.9, 84.3, 84.2, 73.2, 72.9, 70.2, 69.4, 68.5, 55.0, 54.8, 42.5, 41.5, 41.2, 39.8, 38.5, 38.0, 29.3, 29.1, 28.7, 28.3, 26.1, 24.4, 21.6, 20.5, 18.4, 18.1, −3.6, −3.7, −4.0. *m/z* (MS-ESI) 497 $[M+Na]^+$. HRMS (ESI) calcd for $C_{27}H_{42}O_3SiSNa$: 497.2521. Found: 497.2511.

*4.1.27. (S)-3-((R)-2-(tert-Butyldimethylsilyloxy)dec-9-ynyl)-5-methylfuran-2(5H)-one [**41**].* To a solution of the alkylated product **40** (924 mg, 1.95 mmol) in DCM (5 mL) cooled to 0 °C was added *m*-CPBA (370 mg, 2.14 mmol) portionwise over 30 min. The reaction was quenched by adding saturated aq Na_2SO_3 (5 mL). The layers were separated, the aqueous layer was extracted with DCM (10 mL). The combined organic layers were washed with saturated aq NaHCO3 (10 mL), water, brine and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to afford the crude sulfoxides (860 mg, 1.75 mmol) as a diastereomeric mixture in 90% yield. The crude compound was taken ahead to the next step without purification. To a solution of the sulfoxides (860 mg, 1.75 mmol) in toluene (17.5 mL) was added solid Na_2CO_3 (372 mg, 3.5 mmol) and the mixture heated to reflux for 6 h. The reaction mixture was cooled to rt, filtered through a pad of Celite and washed with ethyl acetate. The combined organic layers were evaporated under reduced pressure to afford the crude compound, which was purified by column chromatography using 10% EtOAc/hexane (v/v) as the eluent to give the pure enone **41** (541 mg, 1.48 mmol) in 85% yield as a gummy oil. TLC, R_f 0.25 (15% EtOAc/hexane). $[\alpha]_D^{25}$ +26.8 (*c* 2.25 $CHCl_3$); ν_{max} (KBr) 2928, 2857, 1755, 1073, 836, 775 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.10 (d, *J*=1.5 Hz, 1H), 5.0 (q, *J*=6.8 Hz, 1H), 4.0–3.94 (m, 1H), 2.44 (d, *J*=6.0 Hz, 2H), 2.18 (td, *J*=6.8, 3.0 Hz, 2H), 1.86 (t, *J*=3.0 Hz, 1H), 1.59–1.26 (m, 13 H), 0.90 (s, 9H), 0.08 (s, 3H), 0.05 (s, 3H). δ_C (75 MHz, $CDCl_3$) 173.1, 150.9, 131.0, 84.2, 77.0, 70.0, 68.5, 36.9, 32.9, 29.2, 28.6, 28.3, 26.0, 25.0, 19.1, 18.1, −4.4. *m/z* (MS-ESI) 387 $[M+Na]^+$. HRMS (ESI) calcd for $C_{21}H_{36}O_3SiNa$: 387.2331. Found: 387.2331.

*4.1.28. (S)-3-((R)-10-Bromo-2-(tert-butyldimethylsilyloxy)dec-9-ynyl)-5-methylfuran-2(5H)-one [**42**].* A solution of the enone **41** (900 mg, 2.47 mmol) in acetone (25 mL) was treated at rt with AgNO3 (42 mg, 0.247 mmol) and *N*-bromosuccinimide (528 mg, 2.96 mmol). After 1h, ether (30 mL) was added, and the mixture was filtered through a plug of Celite. The plug was rinsed with ether (20 mL) and the combined organic layers were evaporated under reduced pressure to afford the crude compound which was purified by column chromatography using 10% EtOAc/hexane (v/v) as the eluent to give the pure bromo alkyne **42** (820 mg, 1.85 mmol) in 75% yield as a gummy oil. TLC, R_f 0.25 (15% EtOAc/hexane). $[\alpha]_D^{25}$ +15.9 (*c* 1.5, $CHCl_3$); ν_{max} (KBr) 3449, 2925, 2854, 1747, 1257, 1032 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.08 (d, *J*=1.3 Hz, 1H), 5.0 (q, *J*=6.8 Hz, 1H), 4.01–3.93 (m, 1H), 2.42 (d, *J*=5.7 Hz, 2H), 2.22 (t, *J*=6.8 Hz, 2H), 1.58–1.28 (m, 13H), 0.9 (s, 9H), 0.08 (s, 3H), 0.05 (s, 3H). δ_C (75 MHz, $CDCl_3$) 173.4, 151.1, 131.0, 77.2, 70.0, 36.9, 32.9, 29.2, 28.7, 28.2, 26.0, 25.0, 19.7, 19.1, −4.3. *m/z* (MS-ESI) 466 $[M+Na]^+$. HRMS (ESI) calcd for $C_{21}H_{36}O_3SiNaBr$: 465.1436. Found: 465.1431.

*4.1.29. (S)-3-((R,E)-2-(tert-Butyldimethylsilyloxy)-10-iododec-9-enyl)-5-methylfuran-2(5H)-one [**3**].* A solution of the bromo alkyne **42** (775 mg, 1.75 mmol) and $PdCl_2(PPh_3)_2$ (246 mg, 0.35 mmol) in THF (3.0 mL) was cooled under N_2 to 0 °C. The flask was evacuated, flushed with N_2 and *n*-Bu_3SnH (0.93 mL, 3.5 mmol) was added in one portion. The reaction mixture was stirred at 0 °C for 30 min where TLC examination showed complete disappearance of the starting bromo alkyne. The reaction mixture was cooled to −78 °C and a solution of I_2 (577 mg, 2.28 mmol) in DCM (30 mL) was added dropwise over 20 min, such that a dark brown color persisted. The mixture was quenched with saturated aq $NaHCO_3$ (10 mL) and saturated aq $Na_2S_2O_3$ (10 mL) solutions. Ethyl acetate (10 mL) was added and the mixture was stirred for 30 min at rt and extracted with ethyl acetate. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated. Purification by silica gel chromatography using 10% EtOAc/hexane (v/v) as the eluent furnished the vinyl iodide **3** (602 mg, 1.23 mmol) in 70% yield as a clear, colorless syrup. TLC, R_f 0.2 (15% ethyl acetate/hexanes); $[\alpha]_D^{25}$ +12.8 (*c* 2.0, $CHCl_3$); ν_{max} (KBr) 2922, 2852, 1759, 1461, 1070 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.13 (d, *J*=1.3 Hz, 1H), 6.56–6.45 (m, 1H), 5.97 (dd, *J*=14.4, 1.3 Hz), 5.01 (q, *J*=6.6 Hz, 1H), 4.02–3.93, (m, 1H), 2.43 (d, *J*=5.3 Hz, 2H), 2.08 (q, *J*=7.2 Hz, 2H), 1.49–1.26 (m, 13H), 0.90 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H). δ_C (75 MHz, $CDCl_3$) 173.9, 151.3, 146.5, 130.8, 77.3, 74.4, 70.3, 36.8, 35.9, 32.7, 29.4, 28.8, 28.2, 25.9, 24.9, 19.0, −4.4. *m/z* (MS-ESI) 515 $[M+Na]^+$. HRMS (ESI) calcd for $C_{21}H_{37}IO_3SiNa$: 515.1454. Found: 515.1451.

*4.1.30. Attempted synthesis of compound **44**.* (a) To a solution of compound **33** (56 mg, 0.07 mmol) in anhydrous THF (1 mL) cooled at 0 °C was added dropwise a solution of 9-BBN dimer (0.105 mmol in 1 mL THF). The solution was stirred at 0 °C until complete conversion of the starting alkene (approximately 2 h, followed by TLC). In another round bottomed flask, a suspension of K_3PO_4 (22 mg, 0.105 mmol) and iodo compound **3** (45 mg, 0.09 mmol) in freshly distilled dioxane (1.5 mL) was degassed for 30 min by bubbling nitrogen. The solution of trialkylborane and $Pd(PPh_3)_4$ (4 mg, 0.0035 mmol) was then added to the iodide solution and the reaction mixture was heated for 8 h at 85 °C. After cooling to rt, the unreacted borane was oxidized by addition of an aqueous solution of sodium acetate (0.01 mL, 3 M) and hydrogen peroxide (30%, 0.01 mL). After 1 h of stirring at rt, the red solution was diluted with diethyl ether and washed with a saturated aq NH_4Cl and brine. The combined organic extracts were dried over Na_2SO_4. The organic layer was evaporated under reduced pressure to afford the crude product, which was found to be a complex product mixture.

(b) To a solution of **33** (56 mg, 0.07 mmol) in THF (0.9 mL) cooled to 0 °C was added a solution of 9-BBN–H dimer (25 mg, 0.105 mmol) in THF (0.5 mL), and the resultant solution was stirred at rt for 70 min. In a separate flask, a solution of (*E*)-vinyl iodide **3** (45 mg, 0.09 mmol) in DMF (0.7 mL) was prepared. To this solution were added $PdCl_2(dppf)\cdot CH_2Cl_2$ (6.5 mg, 0.009 mmol), Ph_3As (3.0 mg, 0.009 mmol), and 3 M aq Cs_2CO_3 solution (0.045 mL, 0.13 mmol). The resultant mixture was stirred at rt for 15 min before it was treated with the above trialkylborane solution. After being stirred at rt overnight, the resultant mixture was diluted with diethyl ether and washed with H_2O. The aqueous layer was extracted with diethyl ether. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. A complex product mixture was obtained.

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Supplementary data

Experimental procedure for the preparation of the mono benzoate-mono mandelate ester of diol **36** and its enantiomer prepared using D-proline is detailed. Copies of ^1H and ^{13}C NMR spectra are available. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2011.07.079.

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34. The reason for the failure of the reaction is unclear, though the reaction of **3** with an allylic alcohol protected as its triethylsilyl ether possessing a long alkyl chain, a substrate much simpler to **33**, afforded the desired coupling product.